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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte
LARA MADISON, GJALT W. HUISMAN, OLIVER P. PEOPLES

Appeal 2008-0228
Application 09/235,875
Technology Center 1600

Decided: May 29, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 6, 7, 10, 14, 16-21 and 35-39. We have jurisdiction under 35 U.S.C. § 6(b). Claim 1 is representative of the claims on appeal, and reads as follows:

1. A method for the biological production of polyhydroxyalkanoate containing 3-hydroxyhexanoate comprising

providing genetically engineered bacteria expressing a 3-ketothiolase gene encoding an enzyme that converts butyryl-CoA and acetyl-CoA to 3-ketohexanyl-CoA, a reductase gene that encodes an acetoactyl-CoA reductase enzyme that converts 3-ketohexanoyl-CoA to 3-hydroxyhexanoyl-CoA, and a gene that encodes polyhydroxyalkanoate polymerase that polymerizes 3-hydroxybutyrl-CoA and 3-hydroxyhexanoyl-CoA, wherein the enzymes are expressed in sufficient amount to produce polyhydroxybutyrate-co-3-hydroxyhexanoate, wherein the bacteria can utilize butanol or butyrate and the bacteria will produce polyhydroxybutyrate-co-3-hydroxyhexonate.

We reverse.

BACKGROUND

According to the Specification, it "has been discovered that biological systems for the production of PHAs [polyhydroxyalkonates] containing 3-hydroxy-co-hydroxyhexanoate (3H-co-HH) can be improved by using transgenic organisms with faster growth rates and/or by genetically engineering these organisms to produce the co-monomer 3-hydroxyhexanoic acid from cheaper feedstocks, such as butyrate or butanol." (Spec. 5)

The Specification teaches further:

> [M]icroorganisms which do not normally produce the storage polymer PHAs are genetically engineered to produce PHAs by the introduction of a PHA synthase gene and additional transgenes selected from the group comprising genes encoding ß-ketothiolase, acetoacetyl-CoA reductase, β-ketoacyl-CoA reductase, enoyl-CoA hydratase and β-hydroxyacyl-ACP-coenzymeA transferase. The genes are preferably selected on the basis of the substrate specificity of their encoded enzymes being beneficial for the production of the 3HH polymers.

> Useful mutations that can be used to produce 3-hydroxyhexanoic monomers from more economic feedstocks, such as butyrate or butanol, are described. These mutants can be readily generated in bacteria suitable for practicing the described invention by standard techniques known to those skilled in the art.

(*Id.* at 5-6.)

Moreover, according to the Specification, for "efficient PHA synthesis in recombinant *E. coli* strains, it is crucial that the expression of all the genes involved in the pathway be adequate. To this end, the genes of interest can be expressed from extrachromosomal DNA molecules such as plasmids, which intrinsically results in a copy-number effect and consequently high expression levels, or they can be expressed from the chromosome." (*Id.* at 7.)

DISCUSSION

Claims 37, 38, and 39 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

According to the Examiner, the "claims are drawn to methods requiring expression in bacteria of unspecified fatty acid biosynthetic enzymes from *Norcardia salmonicolor*, an enzyme that epimerizes S-3-hydroxyhexanoyl-CoA to R-3-hydroxyhexanoyl-CoA from an unspecified source and of an unspecified structure, or the FaoAB complex from *Pseudomonas putida* of unspecified identity." (Ans. 5.)

The Examiner asserts that while Appellants "describe[ ] by incorporation through reference genes encoding the FaoAB multimeric complex from *Pseudomonas fragi* and the FadAB (i.e. FaoAB) multimeric

complex from *E. Coli* that possesses an activity that epimerizes S-3-hydroxyhexanoyl-CoA to R-3-hydroxyhexanoyl-CoA," Appellants "do[ ] not describe any genes encoding fatty acid biosynthetic enzymes from *Norcardia salmonicolor* or the enzymes; or any gene encoding an enzyme that epimerizes S-3-hydroxyhexanoyl-CoA to R-3-hydroxyhexanoyl-CoA or the enzyme; or genes encoding the FaoAB from *Pseudomonas putida* or the enzyme complex." (*Id.* at 5-6.)

Appellants argue that the prior art, such as can be obtained searching the Medline database, as well as the Specification (p. 14, ll. 19-21), indicates that the amino acid sequences encoding the claimed enzymes are known (Reply Br. 3). According to Appellants, citing Peoples,[1] the skilled artisan "knows what fatty acid biosynthetic enzymes are . . ., and the [S]pecification describes at least one gene from *N. salmonicolor* involved in the fatty acid biosynthetic pathway." (R. Br. 4.) Appellants note further that epimerases were also known in the art (*id.*).

"The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance." *In re Edwards,*, 568 F.2d 1349, 1354 (CCPA 1978). A written description of an invention involving a chemical genus, like a description of a chemical genus, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). While "examples explicitly covering the full scope of the claim language" are not typically required, a sufficient number of representative species must be included "to demonstrate that the [applicants] possesses the full scope of the invention."

[1] Peoples et al., U.S. Patent No. 6,586,658 B1, issued July 1, 2003.

LizardTech, Inc. v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005). This requirement applies not only to compositions of matter, but to methods as well. *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004). However,

> the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

We agree with Appellants that the written description requirement has to be considered with the existing knowledge in the prior art (*see, e.g.*, Peoples; *see also* Ans. 12 (findings regarding claim 38) and Ans. 17 (findings regarding claims 37 and 39)) which establishes that the claimed enzymes and their sequences were known prior to the application filing date, and find that claims 37, 38, and 39 meet the requirement of the written description requirement. The rejection is therefore reversed.

Claim 39 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention.

According to the Examiner, claim 39 "recites the limitation 'wherein the enzymes' in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 38 is drawn to a single enzyme, it is not clear which enzyme is being claimed in claim 39." (Ans. 7.)

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1987).

We agree with Appellants that the skilled artisan would understand the metes and bound of the claims, and acknowledge that they will correct the typographical error and amend "enzymes" to recite "enzyme" in claim 39 (Reply Br. 6). The rejection is therefore reversed.

Claims 1, 7, 10, 14, 16, 18-21, 36, and 38 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Fukui.[2]

Fukui is cited for teaching "a method for producing polyhydroxyalkanoates containing 3-hydroxyhexanoate by transformation of a bacteria *Alcaligenes eutrophus* (now called *Ralstonia eutropha* of claim 14) with a gene (*phaC*) from *Aeromonas caviae* (claim 7) encoding a PHA (polyhydroxyalkanaote) synthase (i.e. polymerase) that polymerizes polyhydroxybutyrate-co-3-hydroxyhexanoate i.e. HB-co-3HH (claim 1)." (Ans. 10). Fukui is also cited for teaching the "production of

[2] Fukui et al., "Cloning and Analysis of the Poly(3-Hydroxybutyrate-co-3-Hydroxyhexanoate) Biosynthesis Genes of *Aeromonas caviae*," *J. of Bacteriol.*, Vol. 179, pp. 4821-4830 (1997).

polyhydroxyalkanoates containing 3-hydroxyhexanoate by transformation of *A. eutrophus* and *Pseudomonas putida*." (*Id.*).

The Examiner relies on Haywood[3] to demonstrate that *R. eutropha* (as described in Fukui) inherently expresses a 3-ketothiolase gene, as well as a reductase gene (Ans. 10-11). As to the utilization of butyrate, the Examiner relies on Schubert[4] (p. 5845, Fig. 2, on the left side just before enzyme 1) and Doi (Summary, lines 1-5)) to demonstrate that the same bacteria can utilize butyrate.

It is axiomatic that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Appellants argue that the claimed method is very different from that of Fukui, as in Fukui, different pathways and enzymes are utilized (App. Br. 11). According to Appellants, as demonstrated by Schubert (relied upon by the Examiner to demonstrate that *R. eutropa* comprises an endogenous 3-keto-thiolase gene), "there is no mention . . . of any enzyme in *R. eutropha*, catalyzing the formation of 3-keto-hexanoyl-CoA from butyryl-CoA and acetyl-CoA." (App. Br. 12.)

Appellants assert that "[a]bsent evidence that these organisms express *all the claimed* enzymes required to produce the necessary substrates to

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[3] Haywood et al., "Characterization of two 3-ketothiolases possessing differing substrate specificities in the polyhydroxyalkanoate synthesizing organism *Alcaligenes eutrophus*," *FEMS Microbiology Letters*, Vol. 52, pp. 91-96 (1988).

[4] Schubert et al., "Cloning of the *Alcaligenes eutrophus* Genes for Synthesis of Poly-β-Hydroxybutyric Acid (PHB) and Synthesis of PHB in *Escherichia coli*," *J. Bacteriol.*, Vol. 170, No. 12, pp. 5837-5847 (1988).

produce poly(hydroxybutyrate-co-3-hydroxyhexonate) from butanol or butyrate, . . . the prior art does not inherently disclose the claimed method." (Reply Br. 6.) Appellants assert further that the

> claims require not only that the organism express the requisite thiolase, but also that the enzymes be expressed in sufficient amount to produce polyhydroxybutyrate-co-3-hydroxyhexonate from butanol or butyrate as the carbon source. The Examiner cited Schubert as evidence that *R. eutropha* comprises an endogenous 3-keto-thiolase gene (phbA). While this confirms that such an enzyme was known, it does not disclose that those skilled in the art had combined it with the other necessary enzymes to produce a copolymer of a short chain substrate, butyrate, with a long chain substrate, hexanoate, in a single organism, provided only with a short chain substrate, butyrate or butanol.

(*Id.* at 8.)

We recognize that during prosecution before the Office, claims are to be given their broadest reasonable interpretation consistent with the Specification as it would be interpreted by one of ordinary skill in the art. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). Claim language, however, "should not be treated as meaningless." *Bicon, Inc. v. The Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006). Moreover, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Philips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc).

Claim 1 (emphasis added) is drawn to:

> A method for the biological production of polyhydroxyalkanoate containing 3-hydroxyhexanoate comprising
>
> providing genetically engineered bacteria expressing a 3-ketothiolase gene encoding an enzyme that converts butyryl-

> CoA and acetyl-CoA to 3-ketohexanyl-CoA, a reductase gene that encodes an acetoactyl-CoA reductase enzyme that converts 3-ketohexanoyl-CoA to 3-hydroxyhexanoyl-CoA, and a gene that encodes polyhydroxyalkanoate polymerase that polymerizes 3-hydroxybutyrl-CoA and 3-hydroxyhexanoyl-CoA, wherein the enzymes are expressed in sufficient amount to produce polyhydroxybutyrate-co-3-hydroxyhexanoate, wherein the bacteria can utilize butanol or butyrate and the bacteria will produce polyhydroxybutyrate-co-3-hydroxyhexonate.

According to the Examiner, the limitation "wherein the bacteria can utilize butyrate or butanol" is given no patentable weight[5] because "it points to an inherent property of the bacteria and not a feature of the method such as an active method step." (Ans. 19.) We, however, interpret the claim as requiring that when butanol and/or butyrate are present, the enzymes recited by the claim; *i.e.*, a 3-ketothiolase gene encoding an enzyme that converts butyrl-CoA and acetyl-CoA to 3-ketohexanyl-CoA, a reductase gene that encodes an acetoactyl-CoA reductase enzyme that converts 3-ketohexanoyl-CoA to 3-hydroxyhexanoyl-CoA, and a gene that encodes polyhydroxyalkanoate polymerase that polymerizes 3-hydroxybutyrl-CoA and 3-hydroxyhexanoyl-CoA; are to be expressed by the genetically-engineered bacteria in sufficient quantities to catalyze the reactions recited in producing polyhydroxybutyrate-co-3-hydroxyhexonate using the butanol and/or butyrate as the starting materials.

Given that interpretation, we find that the Examiner has not established by a preponderance of the evidence that the genes are inherently

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[5] The Examiner does note, however, that if the claim were rewritten to recite "wherein the bacteria are fed butanol or butyrate," that he may consider withdrawing the rejection (Ans. 20).

present in the a bacteria *Alcaligenes eutrophus* (now called *Ralstonia eutropha*) and produce the gene products in sufficient quantities to catalyze the reactions recited in producing polyhydroxybutyrate-co-3-hydroxyhexonate using butanol and/or butyrate as the starting materials. Thus, the Examiner has not set forth a prima facie case of anticipation, and the rejection is reversed.

Claims 1, 6, 7, 10, 14, 16-21, and 35-39 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Fukui, Mascarenas,[6] Schubert, Boynton,[7] Voelker,[8] and Appellant's Specification.

Fukui is relied upon as above (Ans. 14-15), while the additional references are relied upon to teach incorporation of the *PHA* polymerase (synthase) gene into the bacterial chromosome; expression of three enzymes from *C. acetobutylicum* that form butyrl-CoA; expression of an acyl ACP-thioesterase; or expression of the FaoAB complex of *P. putida* (Ans. 14-17). Thus, as the references do not remedy the deficiencies of Fukui, this rejection is reversed as well.

We would like to comment, however, on the combination of Fukui with Boynton. The abstract of Boynton is relied upon for teaching "three enzymes from *C. acetobutylicum* that form butyrl CoA (claim 17) transformed into *E. Coli* and *A. acetobutylicum*." (Ans. 15.) According to

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[6] Mascarenas, U.S. Patent No. 5,470,727, issued November 28, 1995.
[7] Boynton et al., "Cloning, Sequencing, and Expression of Clustered Genes Encoding β-Hydroxybutyryl-Coenzyme A (CoA) Dehydrogenase, Crotonase, and Butyryl-CoA Dehydrogenase from *Clostridium acetobutylicum* ATCC 824," *Journal of Bacteriology*, Vol. 178, No. 11, pp. 3015-3024 (1996).
[8] Voelker et al., U.S. Patent No. 5,512,482, issued April 30, 1996.

the Examiner, it would have been obvious to "substitute or augment the three enzymes that form butyryl-CoA inherent to *R. eutropha* as taught by Schubert with the three enzymes from *C. acetobutylicum* that form butyryl CoA as taught by Boynton." (Ans. 17.) As discussed above, however, the Examiner has not established by a preponderance of the evidence that Fukui (as evidenced by Schubert) establishes that the genes are inherently present in the bacterium *Alcaligenes eutrophus* (now called *Ralstonia eutropha*) and produce the gene in sufficient quantities to catalyze the reactions recited in producing polyhydroxybutyrate-co-3-hydroxyhexonate using butanol and/or butyrate as the starting materials. Moreover, as the references do not teach the use of those genes in the pathway of converting butanol and/or butyrate into polyhydroxybutyrate-co-3-hydroxyhexonate, there would have been nothing to motivate the ordinary artisan to engineer those enzymes into the *R. eutropha* of Fukui.

CONCLUSION

In summary, as the Examiner has failed to set forth a prima facie case of unpatentability as to any of the claims, the rejections on appeal are reversed.

REVERSED

Ssc:

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